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Safety and Utility of Endomyocardial Biopsy in Infants, Children and Adolescents: A Review of 66 Procedures in 53 Patients

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The benefits and risks of endomyocardial biopsy in infants, children and adolescents were determined by reviewing the indications for and complications and results of 66 procedures in 53 patients aged 2 months to 20 years. One patient had a pneumothorax, and three had a right ventricular perforation. Ventricular tachycardia developed in four patients; it was treated with lidocaine in three and was self-limited in one. The procedure was unsuccessful in two patients.

Among 25 patients with a prebiopsy diagnosis of idiopathic dilated cardiomyopathy, microscopic features were consistent with cardiomyopathy in 24 (96%) and were normal in 1. Of nine patients with clinically suspected myocarditis, only two (22%) had microscopic evidence of inflammation, and seven had chronic nonspecific features suggestive of dilated cardiomyopathy. Of eight patients with unexplained arrhythmias, six (75%) had microscopic findings compatible with dilated cardiomyopathy and two had myocarditis. Biopsy tissue samples from seven patients with nondilated forms of cardiomyopathy (four hypertrophic, three restrictive) were consistent with the clinical diagnosis in six and were inadequate in one. Cardiac biopsies were also performed in four patients with other disorders. Among the 51 patients with adequate biopsy specimens, microscopic features were considered diagnostic in 5, confirmatory in 44 and not helpful in 2 with normal tissue.

The results indicate that endomyocardial biopsy is safe in infants, children and adolescents. It is useful for the evaluation of cardiomyopathy and specific secondary forms of myocardial disease. There seems to be little correlation, however, between clinical and tissue diagnoses of myocarditis.

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In adults, the utility of endomyocardial biopsy has been established for the diagnosis of acute cardiac transplant rejection, anthracycline cardiotoxicity, myocarditis and certain secondary forms of cardiac disease, including amyloidosis, hemochromatosis, sarcoidosis and various storage diseases (1,2). Moreover, it may be useful for the evaluation of dilated, hypertrophic and restrictive forms of cardiomyopathy, as well as atypical chest pain and idiopathic arrhythmias (1,2). The clinical role of endomyocardial biopsy in infants, children and adolescents, however, is less well established (3–16). The purpose of this study was to assess the usefulness and complications of endomyocardial biopsy in this age group.

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Methods

Study group. During the decade from January 1978 to December 1987, 66 transvenous endomyocardial biopsy procedures were performed at our institution in 53 patients aged ≤20 years. These cases form the study group, and demographic data, including a patient's age, gender and cardiovascular diagnoses, were obtained from a review of medical charts. Endomyocardial biopsies were performed as described by others (6,8,13,17–19), and all specimens were processed routinely for light microscopy. Additional studies in selected cases included transmission electron microscopy, immunofluorescence microscopy and viral cultures.

Diagnostic biopsy criteria. Certain chronic nonspecific biopsy features were considered to be consistent with cardiomyopathy if appreciable ischemic, valvular, hypertensive and toxic forms of heart disease were excluded clinically (1). These features included myocyte hypertrophy, with or without degenerative changes or attenuation, and proliferation or fibrosis of the myocardial interstitium or endocardium. The diagnosis of lymphocytic myocarditis was established with

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Table 1. Age Distribution of 53 Patients Undergoing Endomyocardial Biopsy

	Patients	
Age (yr)	No.	%
<1	4	8
1 to 5	6	11
6 to 10	3	6
11 to 15	13	25
16 to 20	27	51

the Dallas criteria (20,21) and required the presence of an inflammatory infiltrate and evidence of adjacent myocyte injury or necrosis. According to these criteria, the presence of an inflammatory infiltrate without myocyte damage was labeled borderline myocarditis.

Results

General clinical features. Of the 53 patients, 33 were male and 20 were female. Their ages ranged from 2 months to 20 years; 75% were older than 10 years and 51% were older than 15 years (Table 1). For the entire group, the mean age was 13 years (Table 2) and the median age was 16 years. The most commonly recorded clinical features were heart failure, arrhythmias and chest pain (Tables 2 and 3).

Heart disease was familial in five patients, including three with dilated cardiomyopathy and two with hypertrophic cardiomyopathy. Six patients had congenital heart disease, including one case each of Ebstein's anomaly, combined aortic stenosis and insufficiency, bicuspid aortic valve, patent ductus arteriosus, repaired secundum atrial septal defect and complete heart block.

Technical features. Two patients with dilated cardiomyopathy and three with a prebiopsy diagnosis of myocarditis underwent two biopsy procedures each. Among eight patients with idiopathic arrhythmias, two had two biopsies each and two had four biopsies each. Thus, 66 procedures were performed in the 53 patients; 56 were right ventricular and 10 were left ventricular. Entry sites included the right internal jugular vein in 43 cases, the right femoral vein in 19 and the right femoral artery in 4.

The number of biopsy specimens per case ranged from 1 to 10 (mean 5) (Table 4). Adequate tissue for diagnosis was obtained in 64 (97%) of the 66 procedures and in 51 of the 53 patients. The biopsy tissue was considered inadequate in a 15 year old patient with hypertrophic cardiomyopathy (one specimen) and in an 18 year old patient with old myocardial infarction (three specimens, all endocardial).

Complications. A 17 year old patient whose right internal jugular vein was entered developed a right pneumothorax 24 h after biopsy and was treated with thoracostomy tube drainage. The biopsy procedure was complicated by perforation of the right ventricle with the bioptome or transvenous sheath in three patients (aged 6 months, 11 months and 2 years, respectively). In all three, the procedure was performed from the right leg with use of a preformed sheath for bioptome placement. In two, the resulting hemopericardium was treated by pericardiocentesis and autotransfusion. In one, a small pneumopericardium occurred but required no intervention.

Ventricular tachycardia developed in four patients (aged

Table 2. Clinical Features of 53 Patients Undergoing Endomyocardial Biopsy

	Prebiopsy Clinical Diagnosis						
Feature	Dilated CM (n = 25)	Myocarditis (n = 9)	Arrhythmia (n = 8)	HCM (n = 4)	RCM (n = 3)	Other (n = 4)	Total (n = 53)
Age (yr)							
Mean	12	16	14	9	10	17	13
Range	0.5 to 19	2 to 20	6 to 20	0.2 to 18	2 to 14	12 to 20	0.2 to 20
Gender (no.)							
Male	17	6	4	2	2	2	33
Female	8	3	4	2	1	2	20
Male/female ratio	2.1	2.0	1.0	1.0	2.0	1.0	1.7
Symptoms/signs (no.)							
Heart failure	13	3	0	0	3	0	19
Arrhythmia	13	5	8	0	1	1	28
Chest pain	5	4	1	0	0	1	11
Investigation (no.)							
Cardiac cath	20	6	5	4	3	3	41
Echocardiography	19	7	5	4	3	4	42
Both	15	4	5	4	3	3	34
Neither	1	0	3	0	0	0	4

Cath = catheterization; CM = cardiomyopathy; HCM = hypertrophic cardiomyopathy; no. = number of patients; RCM = restrictive cardiomyopathy.

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Table 3. Types of Rhythm Disturbances in 53 Patients Undergoing Endomyocardial Biopsy

Disturbance	Prebiopsy Clinical Diagnosis (no. of patients)						Total No. of Patients
	Dilated CM	Myocarditis	Arrhythmia	HCM	RCM	Other	
Ventricular tachycardia	1	3	7	0	0	0	11
Ventricular premature complexes	6	0	0	0	0	1	7
Supraventricular tachycardia	3	0	0	0	1	0	4
Atrial fibrillation	0	0	1	0	0	0	1
Atrial premature complexes	0	1	0	0	0	0	1
Congenital CHB	1	0	0	0	0	0	1
Long QT interval	1	0	0	0	0	0	1
Tachybradycardia	1	0	0	0	0	0	1
Vasovagal syncope	0	1	0	0	0	0	1
Total	13	5	8	0	1	1	28

CHB = complete heart block; other abbreviations as in Table 2.

9, 12, 14 and 17 years). In three patients, all of whom had a clinical history of recurrent ventricular tachycardia, the arrhythmia was treated with lidocaine. Tachycardia was self-limited in the fourth patient, who had a history of a long QT interval and ventricular premature complexes.

Cardiomyopathy. Thirty-two (60%) of the 53 patients were diagnosed clinically as having cardiomyopathy (dilated in 25, hypertrophic in 4, restrictive in 3). The disorder was familial in five cases (dilated in three, hypertrophic in two). No patient with restrictive cardiomyopathy had a family history of the disease, and none had evidence of peripheral eosinophilia.

Hypertrophy and fibrosis were the most commonly observed abnormalities in biopsy tissue and were considered to be consistent with cardiomyopathy. Myofiber disarray was no more extensive in patients with hypertrophic cardiomyopathy than in those with dilated or restrictive disease. Although only 32 cases had a *clinical* diagnosis of cardiomyopathy, 44 (83%) of the 53 patients had *biopsy* features suggestive of cardiomyopathy (Table 5).

Dilated cardiomyopathy. The ages of the 25 patients with dilated cardiomyopathy ranged from 6 months to 19 years (mean 12 years); 17 (68%) were male. Heart failure and arrhythmias were the most common clinical manifestations (Tables 2 and 3).

Cardiomyopathy was biventricular in 22 patients and predominantly affected the right ventricle in 3. Associated findings included endocardial fibroelastosis in two patients and muscular dystrophy, Ebstein's anomaly, bicuspid aortic valve, congenital aortic stenosis and insufficiency and congenital complete heart block in one patient each.

Among the 25 patients, the indications for biopsy included confirmation of cardiomyopathy in 14 and evaluation for possible myocarditis in 11. Microscopic features consistent with cardiomyopathy were present in 24 (96%) of the 25 patients (Table 5) and were mild in 18 and moderate in 6. In one patient, the biopsy tissue samples were histologically normal. None of the patients had biopsy evidence of myocarditis.

Six (24%) of the 25 patients with dilated cardiomyopathy have since died, four of heart failure and two after cardiac transplantation. Autopsy tissue samples from two patients had evidence of chronic recurrent myocarditis, although biopsy tissue samples had not shown myocarditis in either case.

Table 4. Distribution of Number of Specimens Obtained in 66 Endomyocardial Biopsy Procedures

No. of Specimens per Procedure	Procedure	
	No.	%
1	4	6
2	3	5
3	7	11
4	12	18
5	20	30
6	8	12
7	9	14
8	0	0
9	2	3
10	1	2

Hypertrophic cardiomyopathy. The ages of the four patients with hypertrophic cardiomyopathy ranged from 2 months to 18 years (mean 9 years); two were male and two were female. The clinical manifestation in each patient was a cardiac murmur. Biopsy features were consistent with cardiomyopathy in three patients (Table 5) and were mild in one and moderate in two. In the fourth patient, who was 15 years old, only one small biopsy specimen was obtained and it was considered inadequate for diagnosis. The youngest patient has since died of aspiration pneumonia, and the other three were still alive.

Restrictive cardiomyopathy. The ages of the three patients with restrictive cardiomyopathy ranged from 2 to 14 years (mean 10); two patients were male and one was female.

Table 5. Comparison of Prebiopsy and Postbiopsy Diagnoses in 53 Patients Undergoing Endomyocardial Biopsy

Postbiopsy Diagnosis	Prebiopsy Clinical Diagnosis (no. of patients)						Total No. of Patients
	Dilated CM	Myocarditis	Arrhythmia	HCM	RCM	Other	
Cardiomyopathy	24	7	6	3	3	1	44
Myocarditis	0	2	2	0	0	0	4
Normal	1	0	0	0	0	1	2
Other	0	0	0	1	0	2	3
Total	25	9	8	4	3	4	53

Abbreviations as in Table 2.

All three had clinical features of heart failure, and one had arrhythmias on Holter electrocardiographic (ECG) monitoring. Abnormalities in the biopsy tissue were consistent with cardiomyopathy in all three patients (Table 5) and were mild in two and moderate in one. There was no history of peripheral eosinophilia, and no eosinophils were observed in the biopsy tissue samples.

The youngest patient has since died suddenly. At autopsy, the heart was characterized by small ventricular chambers with no evidence of disproportionate septal thickening. Myofiber disarray of mild to moderate extent, however, was observed throughout the ventricular myocardium and suggested that this patient had an atypical form of hypertrophic cardiomyopathy.

Myocarditis. Clinically, nine patients were thought to have primary myocarditis. Their ages ranged from 2 to 20 years (mean 16); six were male and three were female. Among the nine patients, five had arrhythmias, four had chest pain, three had heart failure and two were febrile (Tables 2 and 3). Biopsy tissue samples were negative for myocarditis in both patients with fever. In seven (78%) of the nine patients, the biopsy features were consistent with cardiomyopathy rather than myocarditis (Table 5) and were mild in five and moderate in two. In one patient, a 20 year old man, arrhythmogenic right ventricular dysplasia was subsequently diagnosed on the basis of biopsy and clinical findings.

Only two (22%) of the nine patients had biopsy specimens that were positive for myocarditis. One patient, a 19 year old man with mild lymphocytic myocarditis, received no immunosuppressive therapy and is currently asymptomatic with no cardiac dysfunction. The other patient, a 17 year old man with mild lymphocytic myocarditis, had a history of drug abuse (alcohol, marijuana, cocaine and amphetamines), and the myocarditis was presumed to be drug-related.

Among the 16 patients with a prebiopsy diagnosis other than myocarditis (dilated cardiomyopathy in 11 and unexplained arrhythmias in 5) but in whom a cardiac biopsy was performed to rule out myocarditis, an inflammatory infiltrate was detected in 2 (13%). A 9 year old girl with syncope and multifocal ventricular tachycardia had mild lymphocytic myocarditis. Although the arrhythmia persisted, results of three subsequent heart biopsies were normal. The patient subsequently died suddenly and unexpectedly, but no autopsy was performed. The second patient, a 17 year old man with ventricular tachycardia and a past history of drug abuse, had borderline myocarditis associated with a mixed nongranulomatous inflammatory infiltrate of neutrophils, eosinophils and lymphocytes. A subsequent heart biopsy demonstrated abnormalities consistent with cardiomyopathy, concordant with the clinical impression.

Unexplained arrhythmias. The ages of the eight patients with unexplained arrhythmias ranged from 6 to 20 years (mean 14); four patients were male and four were female (Table 2). Seven of these patients had ventricular tachycardia, four of whom had syncope and one had chest pain (Table 3). One patient had atrial fibrillation associated with mitral valve prolapse. Two underwent electrophysiologic studies, and one had Holter ECG monitoring.

Biopsy procedures were performed to exclude the diagnosis of myocarditis in five patients (only one of whom had myocarditis in biopsy tissue), to investigate a possible myocardial cause of the arrhythmia in two and to detect changes consistent with cardiomyopathy in one (whose biopsy result showed myocarditis). In six of the eight patients, biopsy features were consistent with cardiomyopathy (Table 5), and the changes were mild in all six. Of the remaining two patients, one had lymphocytic myocarditis and the other had borderline myocarditis (see earlier).

Other disorders. *A 12 year old boy had idiopathic chest pain* and a slightly dilated right ventricle echocardiographically. Biopsy tissue samples were normal.

A 17 year old woman with synovial cell sarcoma had changes of grade 2 doxorubicin (Adriamycin) cardiotoxicity in the biopsy tissue. She subsequently died of heart failure due to doxorubicin cardiotoxicity and viral myocarditis.

An 18 year old woman had evidence of old inferior and inferolateral myocardial infarctions and had premature ventricular complexes. At cardiac catheterization, her coronary arteries appeared normal, and results of ergonovine study were negative. There was no history of drug abuse. Three biopsy samples were obtained and consisted only of fibrotic

Table 6. Summary of Reported Series of Endomyocardial Biopsies in Infants, Children and Adolescents, 1977–1989

Reference	Year	Age of Patients	Gender (male/female)	Prebiopsy Clinical Diagnosis (no. of patients)						
				Dilated CM	Myocarditis	Arrhythmia	HCM	RCM	Other	Total
MacKay et al. (3)	1977	5 mo to 15 yr	10/5	0	0	3	3	0	9	15
Fujita et al. (4)	1979	4 mo to 5 yr	7/3	9	0	0	1	0	0	10
Yutani et al. (5)	1981	1 mo to 11 yr	138/63	0	0	0	0	0	201*	201
Schmaltz et al. (6)	1982	1 mo to 17 yr	—	3	1	0	4	0	6	14
Takahashi et al. (7)	1983	4 to 14 yr	4/4	0	8	0	0	0	0	8
Rios et al. (8)	1984	7 mo to 12 yr	—	10	5	1	0	0	2	18
Pegelow et al. (9)	1984	3 to 18 yr	—	0	0	0	0	0	13†	13
Lewis et al. (10)	1985	1 mo to 15 yr	10/5	15	0	0	0	0	0	15
Mortensen et al. (11)	1986	7 to 16 yr	3/0	0	0	0	3	0	0	3
Saji et al. (12)	1986	5 to 12 yr	5/3	0	8	0	0	0	0	8
Bhargava et al. (13)	1987	6 mo to 19 yr	—	0	0	0	0	0	7‡	7
Schmaltz et al. (14)	1987	2 mo to 17 yr	8/5	13	0	0	0	0	0	13
Chandra (15)	1987	2 mo to 15 yr	14/12	17	3	0	4	1	1	26
Leatherbury et al. (16)	1988	2 mo to 15 yr	10/10	16	2	0	2	0	0	20
Present study	1990	2 mo to 20 yr	33/20	25	9	8	4	3	4	53

*Kawasaki's disease (mucocutaneous lymph node syndrome); †anthracycline cardiotoxicity; ‡cardiac allograft rejection. Abbreviations as in Table 2.

endocardium. Because no myocardium was available for evaluation, the biopsy tissues were considered inadequate for diagnosis.

A 20 year old man had a history of familial carnitine palmitoyl transferase deficiency. Light microscopy of biopsy tissue showed mild changes of hypertrophy and fibrosis, and transmission electron microscopy demonstrated nonspecific mitochondrial degenerative changes.

Discussion

Although transvascular endomyocardial biopsy was described in children in 1978 (17), only a few series (3–16) of cases have since been published (Table 6). Except for one report of the biopsy features in 201 children with Kawasaki's disease (5), the remaining series have each contained <30 cases. In the current investigation, results were presented for 66 biopsy procedures in 53 patients.

Safety and usefulness of biopsy procedure. Endomyocardial biopsy procedures have been performed safely and successfully in patients as young as 1 month (5,6,10). Although ventricular premature complexes frequently occur during manipulation of the bioptome within the right ventricle (17,18), serious complications are rare, even when multiple serial biopsy procedures are performed (13,22). In fact, no complications were observed in several series (6,8,13,16).

De Moor and Human (18) reported transient bradycardia in 2 of 10 patients. Transient myocardial ischemia developed during left ventricular biopsy in 1 of 30 patients described by Lurie (19), and transient loss of the radial pulse occurred in 1 of 18 patients in the series of MacKay et al. (3). Among 16 patients cited by Leatherbury et al. (16), one death occurred as a result of endomyocardial biopsy.

In the present study of 66 biopsy procedures in 53 patients, 1 patient developed a pneumothorax 24 h later and was treated with thoracostomy tube drainage. Perforation of the right ventricular free wall occurred in three patients and required pericardiocentesis in two and no intervention in one. Thus, serious complications occurred during 3 (5%) of the 66 procedures in this study. Ventricular tachycardia developed in four patients and was self-limited in one and readily controlled with lidocaine in the other three.

The success rate for endomyocardial biopsy in children was 82% in the first reported series in 1977 (3). Since 1980, however, the rate of successful procedures in children has been 93% to 100% (6,8,13,15), and it was 96% in the present study. Moreover, biopsy tissues provided diagnostic or confirmatory information in 67% to 96% of the cases (Table 7) (3,6,15,16). Thus, when applied to infants, children and adolescents, transvascular endomyocardial biopsy seems to be a safe procedure that provides clinically useful information in most cases. However, the risk/benefit ratio should be assessed for patients on an individual basis.

As in adults, the procedure has been widely used for the evaluation of acute cardiac allograft rejection and anthracycline cardiotoxicity (9,13). It also has been an effective diagnostic tool in children with unexplained arrhythmias, muscular dystrophy, storage diseases, so-called oncocytic or histiocytoid cardiomyopathy and cardiac tumors (3,8,23–29). Endomyocardial biopsy has found its greatest application, however, in the evaluation of cardiomyopathy and myocarditis (4–8,10–12,14–16,30,31).

Cardiomyopathy. *Idiopathic dilated cardiomyopathy* in children is most commonly associated with congestive heart failure and must be distinguished from other disorders of known causes that produce similar features (32,33). In most

Table 7. Reported Diagnostic Usefulness of Endomyocardial Biopsy in Infants, Children and Adolescents

		Usefulness						
		Diagnostic		Confirmatory		Not Useful		
Reference	Year	No.	%	No.	%	No.	%	Total
MacKay et al. (3)	1977	3	20	7	47	5	33	15
Schmaltz et al. (6)	1982	2	14	10	72	2	14	14
Chandra (15)	1987	10	36	13	46	5	18	28*
Leatherbury et al. (16)	1988	8	40	7	35	5	25	20
Present study	1990	5	10	44	86	2	4	51†

*There were 28 biopsy procedures in 26 patients; †of the 53 patients, 2 had an unsuccessful procedure.

cases, biopsy tissues demonstrate myocyte hypertrophy and interstitial fibrosis, thereby confirming a diagnosis of cardiomyopathy; but these findings are nonspecific and do not provide information concerning possible causes of the disorder (4,10,14–16).

Alternatively, myocarditis and endocardial fibroelastosis, although they may mimic cardiomyopathy, are associated with specific and diagnostic histopathologic lesions (34,35). Certain storage diseases and mitochondrial disorders also may produce congestive heart failure and mimic cardiomyopathy, but they are associated with specific diagnostic features by transmission electron microscopy (27,28,36).

Hypertrophic and restrictive forms of cardiomyopathy in infants and children have overlapping hemodynamic features and may be difficult to differentiate in some patients (37,38). Myocyte hypertrophy and interstitial fibrosis are the most commonly observed microscopic findings in both disorders and are nonspecific lesions. Myofiber disarray, a feature of hypertrophic cardiomyopathy, may be limited to the core of the ventricular septum and may be inaccessible to the bioptome (39).

Transmission electron microscopy, however, has revealed primary mitochondrial disease in one patient with a clinical diagnosis of hypertrophic cardiomyopathy (16) and unique abnormalities of the contractile elements in three patients with restrictive hemodynamics (40,41). Cardiac fibromas also may mimic hypertrophic cardiomyopathy (16).

Although the dilated, hypertrophic and restrictive forms of cardiomyopathy have distinct clinical and autopsy features, their biopsy findings are generally similar and nonspecific (namely, hypertrophy and fibrosis). In some cases, primary mitochondrial or myofibrillar disorders may be observed by transmission electron microscopy, but such findings usually do not alter therapeutic decisions.

Myocarditis. Myocarditis is an inflammatory disorder of the myocardium that is characterized by a leukocytic infiltrate and adjacent myocyte injury that is not due to ischemia (20,21). Lymphocytic infiltrates that occur in areas of fibrosis without myocyte degeneration or necrosis should not be misinterpreted as myocarditis (42).

In adults, there has been little correlation between clinical and biopsy diagnoses of myocarditis (20), and this also seems to be true for infants, children and adolescents. Among 22 pediatric patients with a clinical diagnosis of myocarditis accumulated from five reports (6,7,12,15,16), biopsy features of myocarditis were observed in only 6 (27%). Similarly, in the present study, a tissue diagnosis of myocarditis was rendered in only two (22%) of nine patients who clinically were thought to have myocarditis.

Furthermore, among 73 pediatric patients with a clinical diagnosis of dilated cardiomyopathy derived from six published studies (4,6,10,14–16), myocarditis was observed in biopsy specimens from 8 (11%). It also was diagnosed in one patient who clinically had restrictive hemodynamics (15). In the current investigation, myocarditis was present in 2 (25%) of 8 patients with unexplained arrhythmias, but it was not detected in any of the biopsy tissue samples from 25 patients who clinically were thought to have idiopathic dilated cardiomyopathy.

Whether myocarditis and dilated cardiomyopathy are linked pathogenetically is a controversial topic (43,44). In some cases, cardiomyopathy does seem to be the result of inflammatory heart disease (44), but this is not necessarily the most common scenario. It is possible that most cases of myocarditis are self-limited and that most cases of dilated cardiomyopathy are related to processes other than inflammation.

No less controversial is whether patients with biopsy-proved myocarditis should be treated with anti-inflammatory or immunosuppressive drugs (45–48). Until the results of a multicenter myocarditis trial (49,50) are available, it is our opinion that caution should be exercised before subjecting pediatric patients to endomyocardial biopsy procedures or to potent drug regimens that have not yet been shown to be efficacious.

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